REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Oath/Declaration

The filed declaration was defective because of the absence of inventor Vale's signature. Applicants hereby submit a new declaration containing inventor Vale's signature.

Specification

The specification was objected to for lack of proper sequence identifiers. Applicants submit that the specification has been amended to include proper sequence identifiers.

The 35 U.S.C. §112 Rejection

Claims 1-8 were rejected under 35 U.S.C. §112, first paragraph, for lack of possession of the claimed invention. The rejection is respectfully traversed.

Claim 1 has been amended to recite an isolated and purified DNA that (a) encodes urocortin II protein that has an amino acid sequence of SEQ ID NO: 10 or 11, (b) hybridizes at high stringency conditions to the complementary strand of the isolated DNA of (a), and (c) DNA that differs from the isolated DNAs of (a) and (b) in codon sequence due to the degeneracy of the genetic code. Applicants submit that the present invention has been clearly defined in the claims that correspond to the disclosure in the instant application. Accordingly, Applicants respectfully request that the rejection of claims 1-8 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 4-8 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner contends that a vector is not capable of expressing a DNA. Claims 4 and 6 have been amended to recite a vector comprising the claimed DNA or a vector encoding urocortin II protein. Applicants submit that the claims have been amended to obviate the rejection. Accordingly, Applicants respectfully request that the rejection of claims 4-8 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 1-8 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is traversed.

Claim 1 has been amended as described above. Claim 7 has been amended as helpfully suggested by the Examiner. Applicants submit that the metes and bounds of the claimed invention have been clearly defined. Accordingly, Applicants respectfully request that the rejections of claims 1-8 under 35 U.S.C. §112, second paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed September 4, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Oct 15, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning on page 33, line 1 has been amended as follows:

The current invention is directed to a DNA sequence encoding urocortin II. This sequence may be an isolated and purified DNA that encodes an urocortin II. Alternatively, it may be an isolated and purified DNA which hybridizes at high stringency conditions to the antisense complement of the urocortin II DNA under high stringency conditions (defined as membrane washing at high temperature and low salt concentration functionally equivalent to 0.1 x SSC at 65°C). Finally, the DNA may be an isolated and purified DNA encoding urocortin II but which differs in sequence due to the degeneracy of the genetic code. This DNA will preferably encode a protein of amino acid sequence SEQ ID No: 10 or amino acid SEQ ID ~~No.~~ NO: 11.

Paragraph beginning on page 33, line 13 has been amended as follows:

The instant invention is also directed to a vector capable of expressing the urocortin II. Such a vector consists of DNA

encoding urocortin II and regulatory elements necessary for expression of urocortin II in a cell. In a preferred embodiment, this vector encodes a protein of amino acid sequence SEQ ID No: 10 or amino acid SEQ ID ~~No.~~ NO: 11. The instant invention is also directed to a host cell transfected with and expressing an urocortin II from such a vector. The protein may be expressed in a cell type selected from bacterial cells, mammalian cells, plant cells and insect cells. In a preferred embodiment, the protein is expressed in *E. coli*.

Paragraph beginning on page 34, line 3 has been amended as follows:

The instant invention is also directed to an isolated and purified urocortin II protein encoded from DNA as described above. Preferably, the purified urocortin II has an amino acid sequence corresponding to SEQ ID No: 10 or SEQ ID ~~No.~~ NO: 11.

Paragraph beginning on page 34, line 16 has been amended as follows:

The current invention is also directed to a DNA sequence encoding human urocortin-related peptide. This sequence may be an isolated and purified DNA that encodes human urocortin-related

peptide. Alternatively, it may be an isolated and purified DNA which hybridizes at high stringency conditions to the antisense complement of the human urocortin-related peptide DNA under high stringency conditions (defined as membrane washing at high temperature and low salt concentration functionally equivalent to 0.1 x SSC at 65°C). Finally, the DNA may be an isolated and purified DNA encoding human urocortin-related peptide but which differs in sequence due to the degeneracy of the genetic code. This DNA will preferably have the sequence shown in SEQ ID No: 1 and will preferably encode a precursor protein of amino acid sequence SEQ ID No: 2 which is proteolytically processed to a protein of amino acid sequence SEQ ID ~~No.~~ NO: 3.

Paragraph beginning on page 37, line 8 has been amended as follows:

The instant invention is also directed to urocortin II or human urocortin-related peptide protein in which the standard "L-form" isomeric amino acids are replaced with "D-form" isomeric amino acids. In human urocortin-related protein, substitution of the isoleucine residue corresponding to position 9 of SEQ ID ~~No.~~ NO: 3 with D-isoleucine, D-phenylalanine, and D-Leucine or other D-form

amino acids is particularly useful. Another useful substitution is the replacement of the glutamic acid residue at position 17 of SEQ ID NO: 3 or SEQ ID NO: 11 with D-glutamic acid.

Paragraph beginning on page 39, line 13 has been amended as follows:

In an effort to identify novel CRF-R ligands, a hidden Markov model (HMM) was constructed from a clustal W alignment of known CRF family proteins, including rat/human CRF, rat Ucn, human Ucn, frog sauvagine, and white-suckerfish urotensin I, using the HMMER software package (Sean Eddy, Department of Genetics, Washington University, St. Louis, MO; see ref. 19). This HMM was used to search the public human genome database and a BAC (Genbank accession no. AC005903) derived from chromosome 3p21.3-4 was identified that contained a 109 bp region exhibiting significant sequence homology but which was not a part of a previously identified gene. This region was extended to 621 bp with the identification of a human EST clone that overlapped with this sequence (Genbank accession No. BE622276). The human sequence, however, lacks a consensus proteolytic cleavage site that would allow for C-terminal processing of the peptide. Therefore, the protein was

designated as a human urocortin-related peptide (hURP) sequence. Figure 1 shows the nucleotide (SEQ ID ~~No.~~ NO: 1) sequence of the predicted open reading frame of the human URP protein. This gene encodes a peptide of amino acid sequence SEQ ID ~~No.~~ NO: 2.

Paragraph beginning on page 41, line 10 has been amended as follows:

I V L S L D V P I G L L Q I L L E Q A R A R A A R E Q A T T N A R I L A R V G H C-NH_2 (SEQ ID ~~No.~~ NO: 3).

Paragraph beginning on page 65, line 18 has been amended as follows:

Extensive analysis of other CRF receptor binding proteins has shown that substitution of normal amino acids with D-isomer amino acids or cyclizing amino acids results in increased affinity for CRF-receptors. In particular, an especially useful substitution is replacement of the isoleucine residue corresponding to position 9 of SEQ ID ~~No.~~ NO: 3 or SEQ ID ~~No.~~ NO: 11 with a "D-form" isomeric amino acid, preferably D-isoleucine, D-phenylalanine, and D-Leucine. Likewise, a glutamic acid residue corresponding to position 17 of SEQ ID ~~No.~~ NO: 3 or SEQ ID ~~No.~~ NO: 11 can be replaced with D-glutamic

acid. Cyclizing amino acids can be formed by chemical bonds between the side chains of two or more residues. For example, adjacent glutamic acid and lysine residues can react to form an amide bond producing a lactam ring. Substitution with nonstandard amino acids such as C_α-methylated leucine, C_α-methylated alanine, N-im-benzylhistidine, 4-hydroxyproline, 5-hydroxylysine, 3-methylhistidine, homoserine, and ornithine may also be used to form agonists or antagonists of human urocortin-related peptide.

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (amended) DNA encoding urocortin II selected from the group consisting of:

(a) isolated and purified DNA encoding ~~which encodes~~ urocortin II protein that has an amino acid sequence of SEQ ID NO: 10 or 11;

(b) isolated and purified DNA encoding urocortin II protein, said DNA ~~which~~ hybridizes at high stringency conditions to the complementary strand ~~antisense complement~~ of the isolated DNA of (a) above, wherein high stringency conditions are characterized as

membrane washing at high temperature and low salt concentration functionally equivalent to 0.1 x SSC at 65°C~~, wherein said DNA encodes urocortin II protein~~; and

(c) isolated and purified DNA encoding urocortin II protein, wherein said DNA differs ~~differing~~ from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code~~, and which encodes urocortin II protein~~.

Claim 4 has been amended as follows:

4. (amended) A vector comprising ~~capable of expressing~~ the DNA of claim 1 ~~wherein said vector comprises said DNA~~ and regulatory elements necessary for expression of said DNA in a cell.

Claim 6 has been amended as follows:

6. (amended) A host cell transfected with the vector of claim 4, said vector encodes ~~expressing~~ urocortin II protein.

Claim 7 has been amended as follows:

7. (amended) The host cell of claim 6, wherein said cell is selected from group consisting of a bacterial cell~~s~~, a mammalian cell~~s~~, a plant cell~~s~~ and an insect cell~~s~~.